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10/650,435	08/28/2003	Paul D. Robbins	AP35301 072396.0261	7180
21003 7590 12/21/2006 BAKER & BOTTS L.L.P. 30 ROCKEFELLER PLAZA 44TH FLOOR NEW YORK, NY 10112-4498			EXAMINER SAIDHA, TEKCHAND	
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SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		12/21/2006	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

# Office Action Summary

Application No.

10/650,435

Applicant(s)

ROBBINS ET AL.

Examiner

Tekchand Saidha

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 27-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 27-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

### **FINAL REJECTION**

1. Applicant's response non-compliant amendment in reply filed 11/13/2006 is acknowledged. Applicants' arguments concerning the claim language is reconsidered in the light of the amendment are found to be persuasive. The new claims 27-39 are drawn to the originally elected invention, and are under consideration in this Office Action.
2. Applicant's amendment and arguments filed 11/13/2006, have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).
3. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.
4. ***Claim Rejections - 35 USC § 112*** (first paragraph)

#### ***Written Description***

Claims 27-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to a molecular chaperone and enhancing CFTR channel activity in any cell expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed or type/specificity of the mutation. [It is not clear what sequences make up the CFTR polypeptides]. Further, the base sequence of the CFTR peptide is not described. Therefore without the reference sequence the description of amino acid position 508 being deleted remains not described and unclear because of the known presence of several CFTR from various human clones, *Xenopus*, among others, which may not possess the same sequence or the numbering in order to match the deletion at residue 508.

The specification does not contain any disclosure or description of the structure(s) and/or function(s) of all CFTR polypeptide sequences having the desired characteristics, the claimed genus. The specification discloses a single human CFTR polypeptide species construct that is capable of binding to a cytoplasmic chaperone, such as Hdj2 or Hsc/Hsp70, and enhancing CFTR channel activity in an epithelial cell expressing a mutant CFTR having a deletion of amino acid residue 508, wherein the CFTR polypeptide is linked to a internalizing peptide selected from SEQ ID NO: 1-20, to facilitate the delivery & uptake of the polypeptide into a target cell.

The single disclosed species is not representative of the genus claimed, or is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants' arguments:

Applicants argue that the claims as presently amended address the basis for the rejection. As recited in new claim 27, the invention encompasses a transport-enhancing polypeptide comprising an internalizing peptide operably linked to a CFTR polypeptide having a deletion of amino acid residue 508 of a 1480 amino acid wild type CFTR protein. As set forth in new claim 35, the invention encompasses a transport-enhancing polypeptide comprising a CFTR polypeptide comprising the nucleotide binding domain 1 (NBD 1) and regulatory (R) domains of human wild type CFTR, as well as an internalizing peptide. Support for new claims 27 and 35 may be found in the specification at paragraph 35, lines 3-12; and paragraph 36. Applicants assert that the new claims obviate the basis for the rejection, which should be removed.

Applicants' arguments are considered but not found to be persuasive for the reasons discussed in the rejections. Applicants have failed to discussed any of the issues of the rejections by arguing that the newly claims obviate the basis for the rejection. The rejection is therefore maintained.

5. Rejection of claims 27-34 under 35 U.S.C. 112, first paragraph, is withdrawn in view of Applicants' arguments and the claim amendment reciting specific position of the mutant CFTR polypeptide wherein amino acid residue 508 is deleted. The issue regarding lack of specific sequence as a reference sequence for the deletion at position 508 is covered under written description and under 35 U.S.C. § 112, second paragraph.

6. ***Enablement Rejection***

Claims 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CFTR polypeptide (specific sequence) species construct comprising (a) an internalizing peptide; (b) a nucleotide binding domain 1 of human cystic fibrosis trans-membrane conductance regulator protein and (c) a regulator domain of human cystic fibrosis trans-membrane conductance regulator protein, which enhances CFTR channel activity in a cell expressing a mutant CFTR having a deletion of amino acid residue 508, wherein the CFTR polypeptide is linked to a internalizing peptide selected from SEQ ID NO: 1-20, does not reasonably provide enablement for any cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to any molecular chaperone and enhance CFTR channel activity in any cell type expressing *any mutant* CFTR with no defined structure of the CFTR polypeptide, cell type where expressed or type/specificity of the mutation.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of CFTR polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's

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sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a single known CFTR polypeptide (250,000 base pairs (250Kb))(see specification, page 3) associated with cystic fibrosis as a result of deletion of a phenylalanine residue 508 ( $\Delta F508$ ), and the specific use of internalizing peptide to carry the cargo into the cell, as measured by the presence of functional cargo in the cell.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple deletion or substitution or other modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass cystic fibrosis transmembrane conductance regulator (CFTR) polypeptide molecules comprising amino acid sequences capable of binding to any molecular chaperone and enhance CFTR channel activity in any cell type expressing any mutant CFTR with no defined structure of the CFTR polypeptide, cell type where expressed or type/specificity of the mutation.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of exact nature of the CFTR polypeptide having the desired enzymatic characteristics is unpredictable and the experimentation

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left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' arguments are considered but not found to be persuasive for the reasons discussed in the rejections. Applicants have failed to discuss any of the issues of the rejections by arguing that the newly claims obviate the basis for the rejection. Applicants arguments especially lack details of how one skill in the art would go about preparing any CFTR mutant(s) considering the 1480 amino acids polypeptide. The rejection is therefore maintained.

7. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 27-34, 36 & 37 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27, lines 5-6, recites '..... a polypeptide in which amino acid residue 508 of a 1480 amino acid wild type Cystic Fibrosis Trans-membrane conductance regulator polypeptide... or claim 36, line 2, recites 'amino acid residues 444-841' with no reference sequence(s). The claims are unclear because of lack of reference sequence of the CFTR polypeptide..'. Claims 28-34 & 37 are included in the rejection for failing to correct the defect present in the base claim(s).

Applicants' arguments:

Applicants argue that the amino acid sequence of wild type CFTR is well known, as described in the specification at paragraph 36, and in Sheppard et al., 1999, Structure and function of the CFTR chloride channel, *Physiol. Rev* 79: S23-45 (Submitted in the Information Disclosure Statement filed March 18, 2004). The Examiner further rejects claims 18-23 as being dependent on the base claim 17, and not correcting the defect in claim 17. As the amended claims are definite, as described above, and all claims depending from the amended claims are also definite, Applicants request that the rejection be withdrawn.

Applicants' arguments are considered but not found to be persuasive because when identifying specific positions of a sequence, the specific sequence must be identified by sequence identifier number (SEQ ID NO: ?) in order for a claim be definite. This is because different CFTR from different human clones, *Xenopus*, etc., may not necessarily possess the same sequence or the numbering in order to match the deletion at residue 508 or residues 444-841. Further, Applicants' reference to wild-type CFTR sequence, does not clarify the source; and Sheppard et al. reference does not provide the *specific sequence* as Applicants argue.

8. **35 U.S.C. § 101**

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title".

Claims 27-39 are rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter.

In the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter. *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claim 17 to recite wording such as "An isolated polypeptide".

Applicants argue that the claims have been amended and now recite 'an isolated polypeptide'. However, that is not the case. The claims are still drawn to 'a polypeptide'.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.



Claims 19-20 & 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meacham et al. [The EMBO Journal, 18(6): 1492-1505 (1999), as applied to claims 17-18 & 21 above, and further in view of USP 6,881,825 (Robbins et al. filing date August 31, 2000).

Meacham et al. describe cystic fibrosis transmembrane conductance regulator (CFTR) polypeptides as a chloride ion channel and therefore has CFTR channel activity, and which comprises two membrane-spanning domains (MSDs), two nucleotide-binding domains (NBD) and a regulatory (R) domain. Human DnaJ 2 (Hdj-2) is a co-chaperone of heat shock cognate 70 (Hsc70) which is localized to the cytosolic face of the ER. They report that immature ER forms of CFTR and  $\Delta F508$  CFTR can be isolated in complexes with Hdj-2 and Hsc70, indicating binding. The  $\Delta F508$  mutation is localized in NBD1 and causes the CFTR to misfold. Levels of complex formation between  $\Delta F508$  CFTR and Hdj-2/Hsc70 were  $\sim 2$ -fold higher than those with CFTR. The earliest stage at which Hdj-2/Hsc70 could bind CFTR translation intermediates coincided with the expression of NBD1 in the cytosol.

The teachings of Meacham et al. are described above in paragraph 8. Meacham et al. do not teach the internalizing polypeptides of SEQ ID NO: 1-20 to facilitate uptake and transport of cargo into the cytoplasm.

Robbins et al. teach a number a internalizing polypeptides to facilitate uptake and transport of cargo into the cytoplasm, including the sequences of SEQ ID Nos. 1-3 (claims 22 & 23), which are 100% identical to SEQ ID NO: 4, 5 and 21 respectively of the Robbins patent, as judged by eye-balling the sequences. See Tables 1-5, for example. The reference further teaches secretion leader sequences as well ability of the internalizing peptides to efficiently internalize cargo in wide variety of cell types both *in vivo* and *in vitro*. Robbins et al. further show the ability of the internalizing peptides to efficiently internalize cargo in the cell, e.g., the presence of **CFTR** protein may be demonstrated by the presence of functional chloride ion channel in a cell original lacking CFTR (*see* column 11, lines 66-67 & column 12, lines 1-15). Thus the reference

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specifically uses the internal peptides to transport CFTR polypeptide (the cargo) into the cell.

It would have been obvious to one of ordinary skill in the art to more efficiently express the CFTR polypeptide of Meacham et al. by incorporating the internalizing peptides of Robbins to efficiently carry cargo into the cell, by way of enhanced CFTR channel activity and expression, as such a teaching is not only suggested but is also demonstrated in the works of Robbins et al; and do so with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the teachings of Meacham et al. and Robbins et al. in view of the importance of cystic fibrosis research to humans and more particularly the biogenesis of CFTR polypeptide having enhanced CFTR channel activity. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, *prima facie* obvious.

Applicants arguments:

Applicants disagree with the Examiner, and assert that the claims are not obvious over Meacham et al. in view of Robbins et al. considered separately or in combination. To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art (In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494,496 (C.C.P.A. 1970) states that "All words in a claim must be considered in judging the patentability of that claim against the prior art." The Examiner must also meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See M.P.E.P. §§ 706.020) and 2143. The teaching or suggestion to make the claimed combination and the reasonable

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expectation of success must both be found in the prior art, rather than Applicants' disclosure.

Applicants assert that there would be no motivation to combine the teachings of Meacham et al. and Robbins et al. Meacham et al. describes transfecting cells in vitro with nucleic acids encoding CFTR polypeptides in order to study the polypeptides' chaperone binding characteristics as the polypeptides pass through the ER following translation. Robbins et al. disclose internalizing peptides used to transport a cargo, for example, a protein, into the cytoplasm of a cell. Meacham et al. transfect cells with nucleic acids encoding CFTR polypeptides. The nucleic acids of Meacham et al. are only translated into CFTR polypeptides after they have been introduced into the cells. Applicants respectfully remind the Examiner that "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" (*In re* Mills, 916 F.2d 680, 16 USPQ2d 1430 (FED. Cir. 1990); and M.P.E.P. § 2143.01(111)).

Meacham et al. internalizes nucleic acids encoding CFTR polypeptides, not the CFTR polypeptides themselves. Adding Robbins et al.'s internalizing peptide to Meacham et al.'s CFTR polypeptides would not affect internalization since it is a nucleic acid that is internalized in Meacham et al. The internalizing peptide, like the CFTR polypeptide, would be translated inside the cell after the nucleic acid has already been internalized. Thus, there would be no motivation to combine the teachings of the two references.

Response:

The prior art of Meacham and Robbins clearly (1) suggest or motivate, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations; and so is discussed above.

Applicants further argue that Meacham et al. transfect cells with nucleic acids encoding CFTR polypeptides. The nucleic acids of Meacham et al. are only translated into mutant CFTR polypeptides after they have been introduced into the cells.

Transfecting cells with DNA encoding CFTR (mutant form) polypeptide is a way of introduction of foreign genes into cell, which is no different than 'cell expressing a mutant CFTR' (*see* language of instant Claim 27 or 35).

As far as Applicants' arguments "Adding Robbins et al.'s internalizing peptide to Meacham et al. 's CFTR polypeptides would not affect internalization since it is a nucleic acid that is internalized in Meacham et al."; is not clear, and because expression of DNA construct encoding CFTR polypeptides + internalizing peptide into the cell is done recombinantly. How else is the construct *expressed*? The rejection is therefore maintained for all the reasons of record.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Tekchand Saidha  
Primary Examiner, Art Unit 1652  
Recombinant Enzymes, 02A65 Remsen Bld.  
400 Dulany Street, Alexandria, VA 22314  
Telephone: (571) 272-0940  
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